AMENDMENTS TO THE DRAWINGS

The attached sheets of drawings include changes to Figures 1-5. These sheets, which include Figures 1-5, replace the original sheets including Figures 1-5. In Figures 1-5, previously omitted designations (A, B, C, etc.) for each individual structure have been added in compliance with 37 C.F.R. 1.121(d), showing the proposed changes in red. No new matter has been added.

Attachments: Replacement Sheets

REMARKS

Amendments to the Claims

Claims 23, 41 and 49 have been amended to revise "tumors" to "tumors associated with angiogenesis." The claims are amended to more accurately define the subject matter of the presently-claimed inventions. The claims are supported by the originally filed specification, *e.g.*, page 2, lines 19-26; page 4, lines 20-27 and page 5, line 1 to page 6, line 3. No new matter has been introduced by the amendments, and their entry is respectfully requested. Upon entry of the present amendments, claims 23, 25-31 and 33-71 are pending in this application.

I. The Objection to the Drawings Should be Withdrawn.

On page 3 of the Office Action, the drawings are objected to because they include the newly added designations of structures (A, B, C, etc.).

In response to the objection, Applicant has amended the drawings in compliance with 37 C.F.R. 1.121(d), showing the proposed changes in red. No new matter has been added. Accordingly, Applicant respectfully requests that the objection to the drawings be withdrawn.

II. The Claimed Invention Meets Enablement Requirements

Claims 23, 25-31 and 33-71 are rejected under 35 U.S.C. §112 as failing to comply with the enablement requirement. (pages 4-11 of Office Action). Applicant respectfully traverses the rejection.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention (citing *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993)). Furthermore, "[a] specification disclosure...must be taken as being in compliance with the enablement requirement...unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *Id.* (emphasis added).

Solely to promote the allowance of the case and without acquiescing to the Examiner's rejection, the claims have been amended to recite methods for inhibiting growth, metastasis or recurrence of *tumors associated with angiogenesis*, by administering an

effective amount of thalidomide to human patients. Thus, the pending claims encompass methods for inhibiting formation or growth of tumors associated with angiogenesis in humans, methods for inhibiting metastasis of tumors associated with angiogenesis in humans, and methods for reducing the recurrence of tumors associated with angiogenesis in humans, using an effective amount of thalidomide.

The specification discloses the methods of administration including mode of administration, doses of thalidomide and dosage forms to be used, and specifies the patients to be treated against the diseases associated with angiogenesis including tumors. (*See, e.g.*, page 7, lines 28-35, page 11, lines 9-20, and page 20, line 2 to page 23, line 2). It is also disclosed that thalidomide can be prepared by known synthetic procedures. (*See, e.g.*, page 19 lines 5-20). The specification also discloses working Examples I to III (pages 24-28, chick chorioallantoic membrane (CAM) assay, rabbit cornea angiogenesis assay and inhibition of bFGF induced corneal neovascularization), demonstrating that thalidomide is effective in inhibiting angiogenesis *in vivo*. The inhibitions of angiogenesis by thalidomide are described on page 27 of the specification, and Figures 6 and 7.

Therefore, all that is required for those of ordinary skill in the art to practice the claimed invention is to administer the specified amount of thalidomide using the specified routes of administration to the specified patients, further to and in accordance with the explicit teachings of the present application. In view of the foregoing, the specification provides a sufficient guidance as to inhibiting growth, metastasis or recurrence of tumors associated with angiogenesis, by administering an effective amount of thalidomide. Thus, one skilled in the art would have been able to make or use the claimed invention without undue experimentation.

The Office Action states that working examples are limited to demonstrating anti-angiogenic activity of thalidomide and the fact that thalidomide inhibits angiogenesis does not reasonably suggest that it will be effective in inhibiting tumor growth. (Page 10 of Office Action). Applicant respectfully disagrees.

The specification clearly describes that undesired angiogenesis occurs in certain tumors, and teaches the relationship between the inhibition of undesired angiogenesis and the inhibition of tumor growth. For example, the specification at page 2, lines 19-26; page 4, lines 20-27 and page 5, line 1 to page 6, line 3, states as follows:

> "Persistent, unregulated angiogenesis occurs in a multiplicity of disease states, tumor metastasis and abnormal growth by endothelial cells and supports the pathological damage seen in these conditions. The diverse pathological states created due to unregulated angiogenesis have been grouped together as angiogenic dependent

or angiogenic associated diseases. Therapies directed at control of the angiogenic processes could lead to the abrogation or mitigation of these diseases....

One of the most frequent angiogenic diseases of childhood is the hemangioma.....

Angiogenesis is prominent in solid tumor formation and metastasis. Angiogenic factors have been found associated with several solid tumors such as rhabdomyosarcomas, retinoblastoma, Ewing sarcoma, neuroblastoma, and osteosarcoma. A tumor cannot expand without a blood supply to provide nutrients and remove cellular wastes. Tumors in which angiogenesis is important include solid tumors, and benign tumors such as acoustic neuroma, neurofibroma, trachoma and pyogenic granulomas. Prevention of angiogenesis could halt the growth of these tumors and the resultant damage to the animal due to the presence of the tumor.

It should be noted that angiogenesis has been associated with blood-born tumors such as leukemias. It is believed that angiogenesis plays a role in the abnormalities in the bone marrow that give rise to leukemia-like tumors.

Angiogenesis is important in two stages of tumor metastasis. The first stage where angiogenesis stimulation is important is in the vascularization of the tumor which allows tumor cells to enter the blood stream and to circulate throughout the body. After the tumor cells have left the primary site, and have settled into the secondary, metastasis site, angiogenesis must occur before the new tumor can grow and expand. Therefore, prevention of angiogenesis could lead to the prevention of metastasis of tumors and possibly contain the neoplastic growth at the primary site.

Knowledge of the role of angiogenesis in the maintenance and metastasis of tumors has led to a prognostic indicator for breast cancer....Control of angiogenesis by therapeutic means could possibly lead to cessation of the recurrence of the tumors."

Clearly, the specification describes the nexus between the control of angiogenesis and inhibition of the tumor growth or tumor metastasis.

In addition, where a particular model is recognized as correlating to a specific condition in a given art, the Examiner should accept that correlation, unless the Examiner has evidence that the model does not correlate. *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995); MPEP. § 2164.02. In the specification at pages 24-28 of the present application, Example I (chick embryo chorioallantoic membrane (CAM) Assay), Example II (rabbit cornea angiogenesis assay) and Example III (inhibition of bFGF induced corneal neovascularization) are disclosed. The Examples demonstrate that thalidomide is

effective in inhibiting angiogenesis *in vivo*. The CAM assay and rabbit cornea assay are known in the art to be commonly-used assays for studying anti-angiogenic activity *in vivo*. See *e.g.* Langer *et al.*, *Biotechnology (NY)*, 9(7) (1991), page 630, right column. A copy of Langer *et al.* is submitted herewith.

In particular, Langer identifies the recited tumors (solid tumors, retinoblastoma and hemangioma) as "angiogenesis-dependent diseases." Langer, page 630, Table 1. Moreover, Langer acknowledges the therapeutic value of angiogenesis inhibitors in the treatment of these diseases. Langer, page 630. As such, Applicant respectfully submits that anti-angiogenic activity is correlated to the inhibition of tumor growth and the treatment of the recited diseases.

Thus, the specification supports that the correlations between the claimed methods, the inhibition of angiogenesis and the working examples described in the specification. A sufficient guidance is provided in the specification so as to allow those of ordinary skill in the art to make and use the claimed invention.

Indeed, the articles published after the filing date of the application reported that thalidomide had been being studied and used for treating tumors, based on the discovery of the present inventor that thalidomide inhibits angiogenesis.

For example, Kumar, et al. (Journal of Clinical Oncology, Vol. 22, No. 12, pp. 2477-2488, 2973 (2004)) reports, on page 2478, the second paragraph, that "*the resurge of interest in this drug as an antineoplastic agent in the last decade coincided with two key scientific observations....The other was the discovery that thalidomide possessed potent antiangiogenic properties [by the present inventor D'Amato].*"

Rajkumar (Mayo Clin Proc. July 2004; 79(7):899-903) points to the present invention on page 900, second column, the last two paragraphs, by stating "*D'Amato et al and Kenyon et al noted that thalidomide possessed substantial antiangiogenic properties. On the basis of evidence that antiangiogenesis was an appropriate target for cancer therapy and the fact that thalidomide possessed antiangiogenic properties, researchers at the University of Arkansas treated multiple myeloma with the drug in 1997 and thalidomide was remarkably effective in these patients.*"

Diggle (IJCP, November 2001, Vol. 55, No. 9, pp. 627-631) also reports on page 630, left column, the second paragraph, that "*Cancer was thought to be a target for thalidomide at an early stage. In 1965 two trials of the drug [including Grabstald] in wide ranges of advanced malignancies were published. The results were very disappointing, however D'Amato and colleagues demonstrated the ability of the drug to inhibit angiogenesis (induced by fibroblast growth factor) in a rabbit cornea assay. It was shown that*

angiogenesis inhibition by thalidomide analogues correlated with the teratogenic but not the sedative and immunosuppressive properties of the drug. This evidence was considered to justify the trial of this antiangiogenic drug in cancer again." (emphasis underlined).

The article of D'Amato study (*Proc. Natl. Acad. Sci.*, USA 91, 1994, page 4082-5) mentioned above is submitted herewith. As disclosed in the present application, D'Amato describes that thalidomide was effective in inhibiting angiogenesis *in vivo* in rabbit cornea angiogenesis assay, and concludes that there are clear implications for the use of this drug for treating angiogenesis associated diseases including tumors. *See*, at page 4085.

In view of the foregoing, the art as a whole supports the current use of thalidomide for treating tumors, based certainly in part upon the discovery of the present inventor that thalidomide inhibits angiogenesis. This is evidence that a skilled person in the art can practice the claimed invention without undue experimentation based upon the examples and the specifications.

Applicant respectfully points out that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970). *See* also MPEP § 2164.01(b). (emphasis added). Applicant respectfully submits that the pending claims are enabled, because the specification "contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented." (*See U.S. v. Telectronics, Inc.*, at 785).

Further, as the Examiner is well aware, "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." *In re Brana*, at 1566; MPEP § 2164.02. "A rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence" (*Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)).

Furthermore, Applicant respectfully submits that "compliance with the enablement requirement does not turn on whether an example is disclosed." *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987) cited at MPEP § 2164.02. Even in unpredictable arts, a disclosure of every operable species is not required to satisfy enablement. MPEP § 2164.03. All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art." MPEP § 2164.08. Thus, one of ordinary skill in the art, armed with the information presented in the specification and publication, has adequate guidance to practice the claimed invention.

In sum, Applicant respectfully submits that: (1) the specification provides sufficient information and guidance to those of ordinary skill in the art to make and use the claimed invention; (2) the Examiner did not provide any factual or legal basis to doubt that the claims are enabled; and (3) to the extent any experimentation is necessary, such experimentation is not undue. Therefore, Applicant respectfully requests that the rejection of the claims under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

III. The Claimed Invention is Not Anticipated

Claims 23, 25-30, 33-39, 41-47, 58 and 67-71 are rejected under 35 U.S.C. § 102(b) as being anticipated by Grabstald *et al.* (*Clinical Pharmacology and Therapeutics*, 1965, 6:298-302, hereinafter "Grabstald") (pages 11-12 of Office Action). Applicant respectfully traverses these rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

Instant claims 23, 41 and 49 have been amended to recite "tumors associated with angiogenesis." The amended claims recite methods for inhibiting the formation or growth of tumors associated with angiogenesis (claim 23), methods for inhibiting metastasis of tumors associated with angiogenesis (claim 41), and methods for reducing the recurrence of a tumor associated with angiogenesis (claim 49), by administering an effective amount of thalidomide to human patients, respectively.

On the contrary, Grabstald does not teach or suggest any uses of thalidomide for inhibiting the formation, growth, metastasis or recurrence of tumors associated with angiogenesis. Grabstald reports that thalidomide was administered to 71 cancer patients but it does not teach any objective benefit of the study. Grabstald does not teach or specify that any of the tumors of the patients in the study were "angiogenesis-associated tumors." Moreover, the reference does not provide any evidence of anti-angiogenic activity of thalidomide. Thus, Grabstald is missing the essential elements of the claims, and does not teach each and every element set forth in the claims. Accordingly, instant claims 23, 41 and 49 are not anticipated by Grabstald.

The remaining pending claims are dependent on claims 23, 41 or 49, directly or indirectly. The dependent claims are not anticipated by Grabstald as they recite further elements. That is, Grabstald does not teach or suggest the elements of the claims, such as mode of administrations of thalidomide (claims 25, 35, 43, 52, 59, 61, 63, 65 and 71), dosage

forms of thalidomide (claims 26, 31, 39, 40, 47, 48, 56, 57, 60, 62, 64 and 66), doses of thalidomide (claims 27-29, 36-38, 44-46 and 53-55), or types of tumors (claims 33, 34, 42, 58 and 67-70). Thus, the dependent claims are not anticipated by Grabstald.

In view of the foregoing, the pending claims are not anticipated by Grabstald and this rejection must be withdrawn.

Nonetheless, it is alleged that Grabstald teaches the claimed methods of inhibiting the growth of tumors in human, because thalidomide within the dose recited was used in the treatment of 71 patients including the instantly recited breast cancer, one patient with endometrial carcinoma did not show any apparent progression of the diseases for several months, and one patient with renal cell carcinoma demonstrated objective benefit related to the administration of thalidomide. (Page 12 of Office Action).

The contention is contrary to the plain disclosure of Grabstald, because the reference concludes that "no significant degree of antineoplastic activity was demonstrated....In the absence of more definite evidence of pharmacologic or anticancer effects in man, we conclude that further random trials of this drug against cancer in man are not indicated." (Grabstald, last paragraph of right column, page 301).

As to endometrial carcinoma, Grabstald discloses that only one patient did not show any apparent progression of the diseases for several months, "there was however no decrease in the size of abdominal masses, and after several months the growth of the cancer became apparent and the patient died one year after the onset of therapy" and that "this course is not incompatible with the natural evolution of untreated disease" and "one case of endometrial carcinoma in each of the other two series showed no effect." (Grabstald, page 301, left column, second paragraph). Thus, Grabstald teaches that thalidomide was not effective in the patients with endometrial carcinoma.

Further, as to renal cell carcinoma, Grabstald discloses that only one patient showed regressions of pulmonary metastases after nephrectomy[1] and that "the pulmonary metastases that were first noted to have disappeared in late March, 1963, did not begin to increase in size and number until October, 1963, and then they *grew rapidly during the last month before death.*" (Grabstald, page 301, left column, last paragraph to right column, first paragraph). Grabstald concluded that "*no evidence of objective regressions* was obtained, with exception of one patient with renal cell cancer whose pulmonary metastases disappeared *transiently* after treatment. Since this patient also had a nephrectomy preceding the regression, the

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[1] The term "nephrectomy" means excision of a kidney, according to Dorland's Medical Dictionary, 23rd Ed., page 460.

response may be attributed to this operation." (Grabstald, last paragraph, page 302). Therefore, Grabstald provides no evidence that the administration of thalidomide resulted in the treatment of any metastasis. Further, Grabstald reports that six patients with renal cell carcinoma receiving thalidomide showed no evidence of benefit. (Grabstald, page 301, right column, second paragraph). In fact, Grabstald teaches away from Applicant's invention by demonstrating many patients did not respond.

The Examiner has cited no portion of Grabstald showing that thalidomide is effective against cancer in man. Thus, Grabstald fails to disclose *each and every* limitation of the instant claims and it cannot anticipate the instant claims.

Further, Applicant's analysis of Grabstald is confirmed and supported by various articles published after the earliest filing date of this application by skilled persons in the art. Examples of the publications and the present inventor's article are submitted herewith, which confirm (1) our analysis of Grabstald, (2) the interest in even trying thalidomide as a tumor therapy disappeared for about 30 years due to negative results of studies such as Grabstald, (3) it was the breakthrough made by the present inventor which demonstrated that thalidomide could be used in tumor therapy and re-ignited interest in the drug, and (4) that thalidomide is now being used and studied further as a treatment for tumor.

For example, Glasmacher, et al. (Acta Haematol 2005; 114 (suppl 1):3-7) discloses, on page 3, right column, line 3 from the bottom to page 4, left column, line 3, that "*As early as the 1960s, some researchers started to look at thalidomide's anti-cancer activity, but this research was quickly abandoned as the catastrophe around the drug emerged and the first trials [including Grabstald] gave negative findings. In the 1990s, the antiangiogenic and anti-tumor necrosis factor properties of thalidomide were explored.*" (emphasis underlined).

Kumar, et al. (Journal of Clinical Oncology, Vol. 22, No. 12, pp. 2477-2973 (2004)) reports, on page 2478, left column, lines 7-14, that "*In another study [Grabstald], thalidomide was evaluated in 71 patients with a variety of cancers at doses ranging from 300 to 2,000 mg/d. Except for resolution of pulmonary metastasis in a patient with renal cell carcinoma, no other responses were seen. There was at least one other negative study conducted during that time period. Following these initial unimpressive trials, there was little enthusiasm regarding thalidomide as an antineoplastic agent until the late 1990s.*" (emphasis underlined). Kumar further states that on page 2478, the second paragraph that "*the resurge of interest in this drug as an antineoplastic agent in the last decade coincided with two key scientific observations....The other was the discovery that thalidomide possessed potent antiangiogenic properties [by the present inventor D'Amato].*"

Rajkumar (Mayo Clin Proc. July 2004; 79(7):899-903) describes, on page 899, right

column, line 6 from the bottom to page 900, left column, line 4, that "*In fact, at least 3 large clinical trials involving approximately 200 patients were undertaken in the United States to investigate thalidomide use for treatment of advanced cancer [including Grabstald]. No notable activity was seen with this drug in any of these early trials, and enthusiasm for continuing research of thalidomide as an anticancer agent disappeared for about 3 decades.....thalidomide was proved unsuccessful in the treatment of cancer.*" (emphasis underlined). Rajkumar points to the present invention on page 900, the last two paragraphs "*D'Amato et al and Kenyon et al noted that thalidomide possessed substantial antiangiogenic properties. On the basis of evidence that antiangiogenesis was an appropriate target for cancer therapy and the fact that thalidomide possessed antiangiogenic properties, researchers at the University of Arkansas treated multiple myeloma with the drug in 1997 and thalidomide was remarkably effective in these patients.*"

Diggle (IJCP, November 2001, Vol. 55, No. 9, pp. 627-631) also reports on page 630, left column, the second paragraph, that "*Cancer was thought to be a target for thalidomide at an early stage. In 1965 two trials of the drug [including Grabstald] in wide ranges of advanced malignancies were published. The results were very disappointing, however. ... D'Amato and colleagues demonstrated the ability of the drug to inhibit angiogenesis (induced by fibroblast growth factor) in a rabbit cornea assay. It was shown that angiogenesis inhibition by thalidomide analogues correlated with the teratogenic but not the sedative and immunosuppressive properties of the drug. This evidence was considered to justify the trial of this antiangiogenic drug in cancer again.*" (emphasis underlined).

In sum, the art as a whole dovetails well with the Applicant's analysis that Grabstald does not anticipate the present invention. It must be considered that skilled persons in the art have admitted that Grabstald does not anticipate the use of thalidomide for inhibiting growth of tumors associated with angiogenesis, as recited in the instant claims.

In fact, the Office Action itself admitted that the prior art supports that thalidomide is ineffective in inhibiting tumor growth in humans (page 10, lines 9-11) and a preponderance of the evidence of the prior art suggests that thalidomide is ineffective in inhibiting tumor growth in humans (page 11, lines 9-10).

In view of the foregoing, Grabstald does not anticipate the use of thalidomide for inhibiting growth, metastasis or recurrence of tumors associated with angiogenesis, as recited in the pending claims. Applicant respectfully requests that the rejection over Grabstald be withdrawn.

IV. The Double Patenting Rejection Should Be Withdrawn

Claims 23, 25-29, 31, 33-40, 58-62, 67-68 and 71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-46 of copending Application No. 11/096,155. (Office Action, page 13).

Applicant requests that the rejection be held in abeyance until the claims of the present application are deemed otherwise allowable.

V. The foreign applications issued patents in many countries.

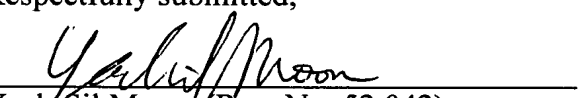
Applicant respectfully request the Examiner's attention to the facts that the foreign applications which correspond to the present application issued patents in many countries for the use of thalidomide in treating tumors associated with angiogenesis. *See, e.g.*, EP Patent No. 0 688 211, EP Patent No. 1 264 597, Canada Patent No. 2157288, Australia Patent No. 676722, New Zealand Patent No. 262676, Mexico Patent No. 215726, Chile Patent No. 40533, and Korea Patent No. 506043. These facts evidence the patentability of the present invention.

VI. Conclusion

Applicant respectfully requests that the above amendments and remarks be entered in the file of this application. Should the Examiner not agree that all claims are allowable, then a further personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application. Please charge any required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: April 19, 2007



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